INTERNATIONAL FORMULA COUNCIL

1100 Johnson Ferry Road, Suite 300 ▪ Atlanta, GA 30342
(404) 252-3663 ▪ Fax (404) 252-0774 ▪ E-mail: info@infantformula.org ▪ www.infantformula.org

December 3, 2009

Dr. Kristina A Thayer
Acting CERHR Director, NIEHS
P.O. Box 12233, MD K2-04
Research Triangle Park, NC 27709
Ph: 919-541-5021
thayer@niehs.nih.gov

Re: Final Written comments on the NTP-CERHR Draft Expert Panel Report on Soy Formula, and request for time for oral public comments during the December 16-18 Expert Panel Meeting (FR Doc. E9–25122)

Dear Dr. Thayer:

These comments are submitted on behalf of all U.S. infant formula manufacturers by the International Formula Council (IFC)*, an international association of manufacturers and marketers of infant formulas whose members are predominantly based in North America.

We wish to make the following observations and comments on the October 19, 2009 draft NTP-CERHR Expert Panel Report on Soy Formula. We also request time for oral public comments during the December 16 Session of the Expert Panel Meeting.

As manufacturers of infant formula, we recognize that our products often provide sole source nutrition at a critical time for growth and development. Thus, we continually work to assure our formulas are safe and of the utmost quality. Through ongoing clinical research and routine review and evaluation of the scientific literature, we also work to assure that our products reflect the latest nutrition advances. Infant formula is one of the most highly regulated food products in the U.S. and we take very seriously all issues related to the safety and efficacy of our products.

It is from this perspective that we reiterate the concerns expressed in our comments dated June 11, 2004, March 1, 2006, June 30, 2006, and December 8, 2006 made during the 2006 NTP-CERHR investigation of the safety of soy formula. IFC believes that the safety of soy-based infant formulas (SIF) has been adequately addressed previously and, from our ongoing review of the scientific evidence, we believe that there is no new information that provides sufficient justification for a re-evaluation of SIF safety. We reaffirm our position that SIF safely provide necessary and appropriate nutrition for normal growth and development in term infants. This view is consistent with that expressed more than a decade ago by the 1997 National Institutes of Health/U.S. Food and Drug Administration (FDA) Panel Meeting on the significance of phytoestrogens in SIF. It is also supported by the 2008 position of the American Academy of Pediatrics (AAP) that the use of SIF is a safe and effective alternative to provide appropriate nutrition for normal growth and development in term infants (1).

Soy has been a celebrated component of human nutrition for almost 5,000 years (2) and soy protein has been used in infant feeding for nearly a century. During this period, SIF have evolved to become

* IFC members are: Abbott Nutrition; Mead Johnson Nutrition; Nestlé Infant Nutrition; and Pfizer Nutrition.

safe and effective alternatives for infants whose nutritional needs are not met with human milk or formulas based on cow's milk (3). From the early 1960s, modern formulas based on soy protein isolates have been fed safely to over 20 million American infants with no greater documented adverse health conditions than infants fed cow milk-based formulas. Since the 2006 NTP-CERHR analysis, in a time of heightened awareness and scrutiny of SIF safety, more than 2 million American infants have been fed soy formula without reports of adverse effects. Modern soy formulas meet all nutritional requirements and safety standards of the AAP Committee on Nutrition (AAP-CON) (4) and the Infant Formula Act of 1980 and its 1986 amendments. They are commonly used successfully in infants with IgE-mediated cow milk allergy, lactose intolerance, galactosemia, as a vegetarian human milk substitute, and in observance of religious practices and traditions.

Many studies support normal growth and development in term infants fed SIF (3, 5-9). Concerns raised on the safety of dietary isoflavones in SIF are mainly based on a relatively small number of animal studies (10). These animal trials are often characterized by inadequate designs, non-physiological dosages and routes of administration, and conflicting results (11, 12). The oral-delivery animal studies are inadequate metabolic models for human infants because they generally do not take into account the animal's conversion of oral daidzein to equol, and equol's higher estrogenic potential. Animal toxicology data can be suggestive in the absence of human exposure experience, but only if the animal models are reliable predictors of effects in humans. The rodent model does not appear to be a reliable model for effects in human infants in this particular case. On the other hand, there are many studies in humans that can be used as reliable indicators of safety.

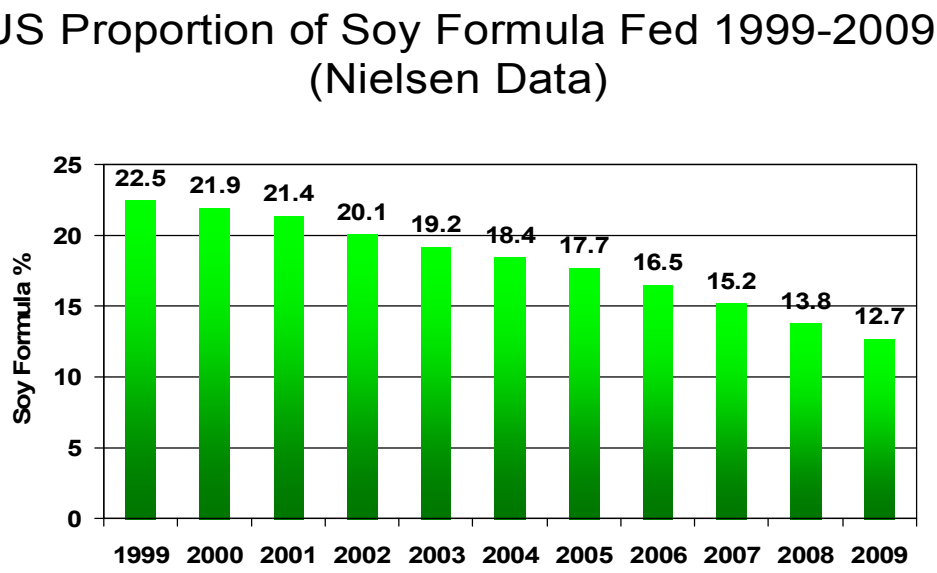
Clinical data available in 2006 showed that SIF do not adversely affect human growth, development, or reproduction. In the 2003 review on the safety of isoflavones, Munro et al. (13) stated clearly, *"There is no conclusive evidence from animal, adult human, or infant populations that indicates that dietary isoflavones may adversely affect human development or reproduction."* Strom et al. (14) evaluated more than 30 developmental and reproductive outcomes in young adults who had participated as infants in blinded randomized clinical trials of SIF or milk-based formula in the first 4 months of life. Strom found similar normal development and reproductive outcomes in both groups with the only differences noted being a slightly prolonged (0.37 day/month) menstrual duration and discomfort with menses, but reproductive outcomes and fertility were not affected. Strom and colleagues note, *"Given the large number of comparisons evaluated in these analyses, the few marginally significant findings may be due to chance,"* and *conclude "the findings of the current study are reassuring about the safety of soy infant formula."* Based on the scientific evidence, Susan Baker, MD, the chair of the AAP-CON in 2001, commented, *"Parents can feel confident that soy-based infant formulas are safe. For over 50 years, millions of babies have grown and developed normally on soy-based formulas. Mother's milk is the best nutrition for babies. The American Academy of Pediatrics policy is that soy formulas are safe and effective for babies who are not being breast-fed and cannot tolerate a cow's-milk formula."* In its 2008 updated recommendations (1) AAP-CON indicates that *"soy protein-based formulas may be used to provide nutrition for normal growth and development,"* although the 2008 recommendation reduces the number of clinical indications for soy formulas compared to the AAP-CON's 1998 recommendations (15). The long history of safe use, the acceptance of soy infant formula feeding by the FDA and the AAP, and long-term human studies indicating an absence of adverse health effects, all seem to clearly demonstrate that soy infant formula is safe and supportive of normal growth, development, and reproduction.

Since 2006 approximately 2.25 million more American infants have been nourished using soy formulas, and over 1,200 infants from around the world have been studied in controlled clinical trials involving soy formula. Neither the continued routine feedings nor clinical trials have generated any reports of toxic effects of SIF; these formulas continue to provide an important, safe, and effective infant feeding alternative. IFC recently analyzed clinical data published since 2005 to determine the amount of new research information available on soy formula toxicology. Results of this analysis are shared below. To put these research reports into context it is important to first document the significance of SIF in US infant feeding, and then describe their clinical indications and use.

US Soy Formula Feeding Rates

IFC wishes to update and expand the data supplied to the Expert Panel on October 13, 2009. Figure 1 shows the SIF percentage of total formula fed (in equivalent feeding units) in the US from 1999 through 2009 (2009 data is year to date through October 24) from AC Nielsen. These data are subject to the same qualifiers listed on page 8 of the Expert Panel Draft Report.

Figure 1.



Unlike the sales of general soy products which have increased from $300 million in 1992 to over $4 billion in 2008, SIF sales have dropped by almost 50% since 1999. Today, a little over one in ten formula feedings are SIF, compared to nearly double that number ten years ago. It is likely that many factors contribute to the decline in SIF use. Nutrition innovations in the last decade have led to the successful development and clinical testing of several new types of cow's milk-based infant formula products, such as those that are lactose free and others based on partially hydrolyzed cow milk protein systems. These new options provide health care professionals with greater flexibility in making infant formula recommendations. However, as documented in Figure 1, the biggest changes in SIF use have occurred within the last few years, coinciding with promotion of the NTP's reviews and reports on soy formulas, and the less supportive position on SIF taken by AAP.

To help parents make the best-informed feeding choices, we urge the NTP to ensure that its review of research on SIF represents clinically relevant scientific evidence. Recommendations that cause undue concern and alarm are not in the best interest of new parents or their infants.

In addition to several important clinical uses of soy formula there are many infants whose parents' cultural, religious, or nutrition practices necessitate a non cow milk-based infant feeding choice. For both parents and healthcare professionals, SIF remain a clinically safe and effective infant feeding option. SIF use is acknowledged as appropriate for cultural, religious, or nutrition practice reasons by AAP-CON (1), ESPGHAN/CON (16), and the Australian Consensus Panel (17).

If parents are unnecessarily alarmed about the safety of feeding SIF, they may choose to feed something else that is neither proven safe nor nutritious. For example, in the popular press there continue to be case examples of parents who make the ill-informed and sometimes deadly choice of feeding their infants soy beverages not designated as infant formula, believing such products are perhaps a more a natural or "healthy" alternative to breast feeding than commercial SIF.

Clinical Indications and use of SIF

There are a number of important medical indications for SIF use. These include:

<u>Disorders of carbohydrate metabolism</u>
AAP-CON (1) and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (16) indicate that SIF are safe and effective for use in infants with severe persistent lactose intolerance including primary (hereditary) lactase deficiency and classic galactosemia. AAP also indicates that SIF can be used successfully in cases of secondary lactase deficiency following acute diarrhea (1).

Managing IgE-mediated cow milk allergy

Using SIF to manage cow's milk-protein allergy (CMA) is controversial, in part due to failure to distinguish IgE-mediated allergy from cell-mediated syndromes. Since 1990, nine well-controlled studies of SIF in CMA patients have been reported (18-26). A meta-analysis shows that 337 of 370 (91.08%) of infants with IgE-mediated CMA were effectively managed with SIF (Table 1).

Table 1.

Study	Infants with CMA fed soy	Infants with CMA developing soy allergy (%)
Bock and Adkins, 1990	54	4 (7.4)
Cantini et al., 1990	20	1 (5.0)
Buts et al., 1993	17	1 (5.9)
Zeiger et al., 1999	93	13 (14.0)
Klemola et al., 2002	80	8 (10.0)
Berger-Achituv et al.,2005	37	1 (2.7)
Agostoni et al., 2007	37	5 (13.5)
Mehr et al., 2008	29	0 (0)
Caminiti et al., 2009	3	0 (0)
TOTAL	**370**	**33 (8.92%)**

The tolerance of soy formula among infants with CMA is slightly lower than hypoallergenic formulas based on extensively hydrolyzed casein (97-98%). However, extensively hydrolyzed formulas have poor palatability (27, 28) that limits compliance and are also more expensive (28). Palatability and expense were not considered in the AAP-CON recommendations (29). Finally, some extremely sensitive CMA patients react severely to extensively hydrolyzed formulas but tolerate SIF (30). Hence, there is a place for SIF in the management of infants with CMA. It is important to note that while AAP-CON (based on data from only two of seven available studies) and ESPGHAN do not recommend SIF for managing IgE-mediated cow milk allergy, the 2008 Australian consensus panel (17) does recommend SIF for this indication.

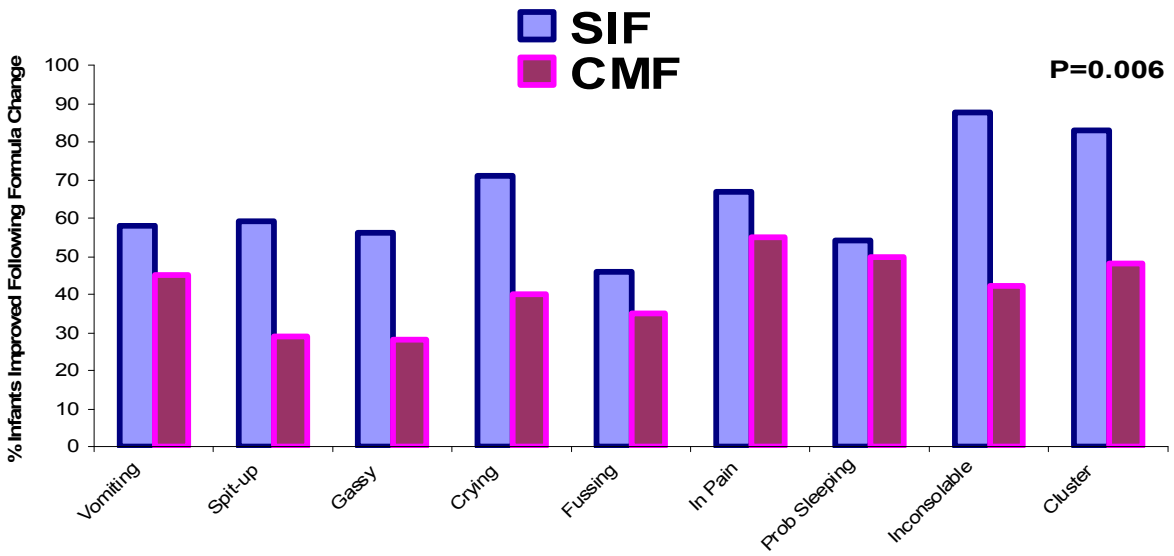
Managing Non-Allergic Cow Milk Formula Intolerance

"Formula intolerance" (FI) is an ill-defined, multi-component syndrome affecting up to 30% of infants during the first nine months after birth. FI symptoms vary in presentation and intensity and include fussiness, gassiness, and spit-up. Physiology of FI is complex, with many known and unknown causes. FI is not life-threatening but it is problematic for parents and infants, and a frequent cause of physician office visits and consultation. Most FI is transient. A substantial placebo effect is seen in clinical studies of FI. Clinical research is also complicated by the subjective nature of symptom evaluation (often performed by parents) and the variability in symptom descriptions (when is "fussiness" colic, when does a "large spit-up" become a small vomit?). Perception of the intensity of FI symptoms can be biased by parental frustration and/or fatigue and there are no validated symptom scales. For these reasons and others there is little high quality clinical research guiding the management of FI. Parents and physicians often make formula changes to relieve symptoms with marginal clinical justifications. FI is a key driver for formula switch decisions by both physicians and parents (31, 32) and often the switch is made to soy formula (32, 33).

Though not supported by large amounts of detailed clinical data, many practicing pediatricians have used SIF for many years to successfully manage FI. Figure 2 shows results from a placebo-controlled experimental subgroup post-hoc analysis of 59 infants from a larger FI management study. Enrollment criteria for the subgroup were FI symptoms serious enough for the treating physician to recommend a formula change. At entry all infants were fed a single brand of commercial cow milk protein-based infant formula. Upon enrollment infants were randomized to receive blinded either SIF or the same commercial cow milk protein-based infant formula they had previously consumed (placebo control). Parents were trained to complete diaries recording FI symptoms including vomiting, spit-up, gassy, crying, fussing, in pain, problems sleeping, and inconsolability. Correlation among various symptoms was analyzed using Cronbach's Alpha Coefficient of Reliability to identify symptoms related to a single clinical element

(cluster). Data was reported group-wise for Day 3 and Day 15 as % of infants with net benefit (symptoms resolved minus symptoms developed). Results show a benefit of switching to soy formula versus the placebo control that was sustained for at least 15 days.

Figure 2. Formula intolerance individual symptoms and Gas + Fussy + Spit-up symptom cluster: % Infants with Day 3 Net Benefit (infants with decreased symptom scores – infants with increased symptom scores) for infants intolerant to a single cow milk-based formula (CMF) at entry who were randomized and "switched" to the same CMF (placebo control) or switched to soy-based formula (SIF). Data on file, Abbott Nutrition.



Similar symptom improvements in FI infants following a switch to SIF were described by Berseth et al. (34). This large (soy n = 82), multicenter, double-blind, randomized, parallel, prospective 28-day feeding trial compared symptom responses when cow milk-based FI infants were blinded and switched to either SIF or a partially hydrolyzed cow milk-based formula (no placebo group was included). Eligible subjects were singleton births, 7-63 days of age, had a minimum birth weight of 2500 g, solely received a full-lactose, intact CMP formula for 7 days before randomization, and were parent-identified as very fussy or extremely fussy in the baseline tolerance evaluation. Results showed similar and significant symptom improvements within 1 day for fussiness, gas, spit-up, and hours crying for both feeding groups. The improvements were stable and lasted for the 4 week study period although the absolute clinical significance of the improvements is unknown without the placebo reference.

Clinical Literature Review 2006 – 2009

Introduction

In the 2008 Federal Register notice announcing the plans for "updated" review of soy formula the new analysis was justified based on CERHR's assertion that "Since 2006, a substantial number of new publications related to human exposure or reproductive and/or developmental toxicity have been published for these substances and CERHR has determined that updated evaluations of genistein and soy formula are needed." (IFC notes that the 2009 Draft Panel Report, is lengthy (791 pages) and in its present form is not simply an "update" of the 214 page 2006 Expert Panel Report, further the content of the 2009 draft report does not emphasize results since the previous report.)

IFC has reviewed the clinical literature published since 2005 to better understand the information specifically related to human exposure or reproductive and/or developmental toxicity of SIF in human infants. IFC has not reviewed the substantial amount of animal data published or otherwise released on

the potential toxicity of SIF, soy isoflavones, or genistein. Briefly, IFC believes that the commonly used animal models fall far short of successfully predicting human infant responses to SIF nutrition. This position is supported for the rodent and monkey models by Gu et al. (68) who demonstrated substantial metabolic phenotype differences between these species and women, and by other recent work from the Arkansas group (Badger, Ronis, et al.) showing gene activation and metabolome differences between humans and rodents in response to isoflavones. It is also important to note that, outside the context of some of the animals used in isoflavone toxicology research rodent chows are typically based on soybean meal and deliver total isoflavones in doses ranging from 80-160 mg/kg body weight per day (12) without apparent ill effects on reproduction and development. Dr. Setchel, in his 2006 guest editorial probably said it best: "*The only appropriate model for postnatal human reproductive development is the human infant."* (12). IFC notes that a number of animal model studies were judged by the Expert Panel to be of "high utility" in assessing the toxicity of SIF while a number of controlled human clinical trials of SIF were judged to be of "no utility." We have read the Panel's explanations justifying these assessments but generally do not agree with the logic. In assessing the true significance of animal model results we suggest a simple test: If the toxic response seen in the animal model accurately predicts a human toxicity of similar magnitude, how would that toxicity be displayed in the clinical histories of the 20 million Americans nourished with modern SIF as infants over the past 40 years? In fact, there is an abundant clinical literature indicating a lack of dramatic negative health consequences associated with soy formula feeding that are predicted by some of these animal model experiments. **IFC believes that a much closer look at human clinical history would be a better indicator of true SIF safety than continued assessments of flawed or even well designed animal model studies that do not truly model the human digestive process of soy formulas.**

IFC Clinical Literature Review Strategy

The goal of the IFC clinical literature review was to identify the *"substantial number of new publications related to human exposure or reproductive and/or developmental toxicity* (that) *have been published for these substances"* since 2006. Only clinical literature was considered and only the "soy formula" (not "genistein" nor "soy foods") search was assessed. PubMed.gov was used as the search engine. Articles with publication dates from January, 2006 through articles appearing in PubMed searches dated August 28, 2009 were identified. The PubMed search was supplemented with expert consultation and other sources which identified additional literature, some first available in mid November, 2009.

Search Results: >2005 Clinical Literature Breakdown

PubMed searches were performed on "soy formula," "soy formula safety," "soy formula reproduction," and soy formula toxicity" with the following results:

Search	# Articles	# Pub > 05	# Human > 05
"Soy Formula"	**620**	**102**	**60**
"Soy Formula Safety"	**45**	**20**	**9**
"Soy Formula Reproduction"	**33**	**9**	**7**
"Soy Formula Toxicity"	**20**	**5**	**1**

The 60 "Human, publication after 2005" articles identified in the "soy formula" search were supplemented with information from other researchers and consultants. The final data base contained 21 peer-reviewed research articles describing new results, 9 Reviews / Meta-analysis articles, 6 Pediatric Society recommendations on SIF use, 5 opinion articles or letters to the editor, and 2 selected studies describing human in vitro or closely related animal data. In addition to articles identified by PubMed other sources yielded an additional 14 meeting abstracts, 3 additional "late-breaking" articles, and 3 reviews. The most important components of the IFC literature review are highlighted below:

Key New and Late-Breaking Results

Cao et al., 2009 (35, 10/19/09 Expert Panel Draft Report [EPDR] ref. 91) report urine, saliva, and blood chemistry results of the SEAD cross-sectional/longitudinal study comparing infants fed human milk (HM), CMF, and SIF. Testing: 166 infants (soy n = 55), 381 urines, 361 salivas, 88 blood samples for genistein, daidzein equol, and hormones. Results: Isoflavone metabolic fate = excretion in urine (genistein in

urine:blood:saliva = 900:40:1), no equol in infant samples, no effect on sex hormone binding globulin, estrone, estradiol, testerone, LH, FSH.
Bernbaum et al. 2009 (36, EPDR ref. 516) report physical findings from the SEAD pilot study on 72 infants (soy n = 24). Exams: genitalia, breast buds, cell maturation index of vaginal wall swabs. Results: measures seem feasible but no group-wise differences in underpowered study. Some believe that the vaginal wall cell maturation index (VWCMI) data suggest a difference between SIF vs CMF/HM. In view of Cao, it might be expected that the large amounts of isoflavones excreted in urine could induce a topical steroidal effect that could be reflected in the VWCMI data. However, in the Bernbaum study, VWCMI is not characterized sufficiently to assess, further it is not a validated indicator of any clinical outcome.

Zung et al. 2008 (37, EPDR ref. 515) report a cross-sectional study of 694 consecutively enrolled private practice infants (soy n = 92). Study groups: SIF-fed versus Milk-fed (both CMF and HM), by parental recall. Year 1: 370 MF, 42 SIF-fed (10.2%), year 2: 232 MF, 50 SIF-fed (17.7%, weaning pattern = HM to SIF). Infants evaluated for the presence of 1.5 cm breast buds, using a non-standard procedure employing a coin as the 1.5 cm standard, by evaluators who were not blinded to the infant treatment group. Results: Table 1 shows no effect during the first year and no effect over years 1 and 2, but a significant difference when only year 2 is considered.

TABLE 1. Diet-related prevalence of breast buds during the first 2 years of life

Both years		First year		Second year	
Milk group (n=602)	Soy group (n=92)	Milk group (n=370)	Soy group (n=42)	Milk group (n=232)	Soy group (n=50)
110 (18.3%)	19 (20.7%)	86 (23.2%)	8 (19.1%)	24 (10.3%)*	11(22%)**

*P<0.001 breast buds prevalence in milk group compared to first year.
** P=0.02 breast bud prevalence in soy vs milk group.

No effects were seen with length of SIF exposure nor SIF starting age. Further, examination of the reported data shows many group-wise comparisons are being made without multiplicity corrections on p values. As demonstrated in Table 2, the Soy-only, Soy with HM, and Soy with HM and CMF groups are not different; rather, the driver for the increased overall frequency of breast buds in the soy group is from the infant group fed Soy with CMF.

TABLE 2. Distribution of soy formula–fed infants (n=92) by food consumption pattern, breast bud prevalence, and length of soy consumption

	Only Soy	Soy with BM and CMF	Soy with CMF	Soy with BM	P
Both years infants (%)	17 (18.5)	22 (23.9)	14 (15.2)	39 (42.4)	<0.05
1st year infants (%)	9 (21.4)	10 (23.8)	6 (14.3)	17 (40.5)	ns
2nd year infants (%)	8 (16.0)	12 (24.0)	8 (16.0)	22 (44.0)	<0.05
Breast bud prevalence (%)	3 (17.6)	5 (22.7)	4 (28.6)	7 (17.9)	ns
Average age, mo	14.1 ±5.1	14.6 ±5.4	13.9 ±6.0	12.6 ±5.0	ns
Length of exposure, mo.	14.0 ± 5.1	7.7 ± 4.8	8.5 ±4.7	8.4 ±3.9	<0.001

BM = breast milk; CMF = cow's milk–based formula.
Comparison vs others by 1-way ANOVA.

The Expert Panel rates this study as of limited utility in assessing SIF safety. Given the non-standard, unblinded evaluations the lack of soy starting age and lack of length of exposure effects, all reported based on parental recall, IFC believes that this study has no value for the evaluation.

Gilchrist et al., 2009 (38, no EPDR ref.) using improved ultrasonography methods measured breast buds, uterus, ovaries, prostate, and testicular volumes in infants at age 4 months to determine if differences exist in hormone-sensitive organ size between infants who were fed SIF (soy n = 39), CMF, or HM. Results: There were no significant feeding group effects in anthropometric or body composition. Among girls, there were no feeding group differences in breast bud or uterine volume. CMF infants had greater ($P < .05$) mean ovarian volume and greater ($P < .01$) numbers of ovarian cysts per ovary than did HM infants. Among boys, there were no feeding group differences in prostate or breast bud volumes. Mean testicular volume did not differ between SIF and CMF boys, but both formula-fed groups had lower

volumes than HM infants. Author's conclusions: Our data do not support major diet-related differences in reproductive organ size as measured by ultrasound in infants at age 4 months, although there is some evidence that ovarian development may be advanced in CMF-fed infants and that testicular development may be slower in both CMF and SIF infants as compared with HM. There was no evidence that feeding SF exerts any estrogenic effects on reproductive organs studied.

Jing et al., 2008 (39, EPDR ref. 520) studied the EEG and Spectral Edge Frequency of an 85 infant subset of the Arkansas Beginnings Study (soy n = 39). Study comparisons include CMF vs SIF, 3 vs 6 months of age, sex, brain location, and right vs left hemisphere. Significant differences were seen for all comparisons EXCEPT CMF vs SIF infants.

Other Clinical Results

Fattal-Valevski et al. 2009a,b, (40, 41, no EPDR refs.) demonstrated problems with language development (soy n = 20) and epilepsy (soy n = 7) in children given defective soy formula that did not contain the required amount of thiamine.

De Mattos et al. 2009 (42, no EPDR ref.) reported that soy-based or casein-based diets do not offer any specific advantage or benefits and do not seem to have a place in the management of persistent diarrhea.

Ngamphaiboon et al. 2008 (43, no EPDR ref.) indicated that switching to SIF is the most frequent and successful strategy for managing cow milk allergy in Thai children (soy n = 162).

Koplin et al. 2008 (44, EPDR ref. = 502) showed that soy consumption is not a risk factor for peanut sensitization. (Soy n = 205). The association between soy consumption and peanut sensitization is not causal but merely a result of preferential use of soy milk in infants with a personal or family history of cow's milk allergy. Future studies should take the confounding effects related to dietary modifications by parents into account when investigating the association between diet and childhood allergic diseases.

Yada et al. 2008 (45, no EPDR ref.) reported a case study (soy n = 1) in which non IgE- mediated CMA with liver dysfunction is resolved with SIF after treatment failure with a casein hydrolysate formula.

Hoffman et al. 2008 (46, EPDR ref. 442) demonstrated that feeding healthy term infants soy-based formula supplemented with DHA and ARA (soy n = 244) from single cell oil sources at concentrations similar to human milk significantly increased circulating levels of DHA and ARA when compared with the control group. Both formulas supported normal growth and were well tolerated.

Ostrom et al. 2006 (47, EPDR ref. 475) showed that SIF with fiber reduces regurgitation (soy n = 89).

Pedrosa et al. 2006 (48, no EPDR ref.) showed that the palatability of formulas is determined by the amount of bitter peptides obtained through hydrolysis. Flavorings and sweeteners may also contribute to palatability.

Hwang et al. 2009 (49, no EPDR ref.) showed that food protein-induced enterocolitis syndrome patients lose intolerance to SIF faster than to CMF (soy n = 12)

Ballmer-Weber et al. 2007 (50, no EPDR ref.) reported DBPCFC data indicating soy allergen reaction thresholds are higher than seen for CMA and that the soy allergen reaction is complex (soy n = 30).

Moreno Villares et al. 2006 (51, no EPDR ref.) reported that SIF supports normal growth and development for infants with CMA (soy n = 70).

Reviews

Joeckel, 2009 (52, no EPDR ref.): "In summary, there is no conclusive evidence that soy formula consumption adversely affects developmental and reproductive health."

Turck, 2007 (53, EPDR ref. 33): SIF provide equivalent nutrition to CMF for term infants, inadequate for preterm. Expresses safety concerns for phytate, aluminum, phytoestrogens. "Soy protein formulae should no longer be extensively used."

Osborne and Sinn 2006 (54, EPDR ref. 285): Cochrane Review, Soy formula for prevention of allergy and food intolerance in infants. Conclusion: Feeding with a soy formula cannot be recommended for prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance. Further research may be warranted to determine the role of soy formulas for prevention of allergy or food intolerance in infants unable to be breast fed with a strong family history of allergy or cow's milk protein intolerance.

Kumar, 2007 (55, no EPDR ref.): GORD in Children: Reports “moderate-quality evidence” that SF with added fiber are more effective than CMF in reducing the frequency of regurgitation at 7-28 days in GORDs patients.

Cordle, 2007 (2, no EPDR ref.): Soy formula for managing infant food allergy and intolerance. SF useful for: Disorders of CHO metabolism, non- allergic CMF intolerance, management of CMF allergy, ethical & religious reasons, 7 contraindications also listed.

Donovan, 2009 (56, no EPDR ref.): Soy formula and Isoflavones and the developing intestine. “Thus, soy isoflavones are bioactive within the neonatal intestine and may reduce the severity of RV (rotavirus) infections.”

Ozdemir, 2009 (57, no EPDR ref.): Food intolerances in childhood.

Williams, 2008 (58, no EPDR ref.): What's new in atopic eczema? An analysis of the clinical significance of systematic reviews on atopic eczema published in 2006 and 2007.

Hill, 2007 (59, no EPDR ref.): The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Article includes comparative (and favorable) soy data.

Allen, 2006 (60, EPDR ref. 281): Food allergy in childhood.

Rozman, 2006 (10, EPDR ref. 15): NTP-CERHR expert panel report on the reproductive and developmental toxicity of soy formula.

Zuidmeer, 2008 (61, no NTP ref.): The prevalence of plant food allergies: A systematic review.

<u>Pediatric Society Recommendations</u>
Bhatia 2008 (1, EPDR ref. 40): Use of soy protein formulas in infant feeding. Deletes recommendation for CMA application. Overstates soy usage (25% vs ~12% actual) and CMA reaction rates (10-14%, 2 studies, 173 patients vs 8.9%, 9 studies 370 patients actual).

Greer, 2008 (62, no EPDR ref.): American Academy of Pediatrics recommendations on the effects of early nutritional interventions on the development of atopic disease. SIF not recommended for preventing atopic disease.

ESPGHAN Committee on Nutrition, 2006 (16, EPDR ref. 34): Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. Lists specific but limited recommendations for SIF usage.

Kemp 2008 (17, EPDR ref. 286): Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion. Positive for SIF use in CMA infants older than 6 mo.

Chouraqui, 2008 (63, no EPDR ref.): French Society of Pediatrics, Committee on Nutrition. Feeding during the first months of life and allergy prevention. Soy based formulae are not recommended for allergy prevention.

Comite de nutrition de la Societe francaise de pediatrie, 2007 (64, no EPDR ref.): Evidence-based dietetics: what has to be kept in mind for the prescription of infant formulae and follow-on formulae in 2007th?

Published Opinions

Setchell 2006, (12, no EPDR ref.): Assessing Risks and Benefits of Genistein and Soy. A listing of the logic defects in much of the current approach to assessing soy safety: "What is needed is a move toward prospective studies to demonstrate the risk/benefit of soy and its bioactive constituents, whether isoflavones, protein, or other components, rather than more animal studies that will unquestionably show many of the same effects already well documented. Might there be long-term health benefits from early feeding of soy formula or soy foods to children? Until such studies are executed and data available, there will be no resolution on this issue, and we face the prospect of throwing the baby out with the bathwater. Common sense should prevail."

Johnson 2008, (65, no EPRD ref.): Effects of soy protein-based formula in full-term infants. "Are there long-term detrimental effects of SIF?" "No."

Badger 2009, (66, no EPDR ref.): The health implications of soy infant formula. After 5 years of a 6 year SIF vs CMF vs HM study, no indications of adverse effects in the SIF infants. Also, appropriate (pig) animal studies show several health benefits without adverse effects.

Human In Vitro and Related Animal Data

Andres 2007, (67, no EPDR ref.): Isoflavones at concentrations present in soy infant formula inhibit rotavirus infection in vitro. Genistein seems to be the active component. Mechanism is by inhibition of viral attachment and modulating a post-binding step.

Gu 2006, (68, EPDR ref. 169): Metabolic phenotype of isoflavones differs among rats, pigs, monkeys, and women. Equol production is a major difference. "…the overall metabolic profile of pigs was closer to that of women than that of rats or monkeys."

Conclusion

Clinical literature published since 2005 describes an array of new clinical experiments involving over 1,200 subjects. Results indicate the presence or absence of various health benefits. Aside from the well known potential of soy formula (or any intact protein-based formula) to induce intolerance or soy allergy, none of the studies report toxic effects for soy formula**. IFC assesses this substantial number of new publications related to human exposure to indicate no new data identifying potential toxic effects of SIF-based infant nutrition.**

Specific Comments on Critical Data Needs:

IFC would like to reiterate some general comments made in 2006 about the incompleteness of the animal data reviewed in the Soy Formula Draft Report. After highlighting this concern in 2006 we are again disappointed that the Expert Panel did not include any agricultural experts. We remind CERHR that soy protein, in the form of soybean meal (typically with isoflavone levels far exceeding those of soy protein isolates used in human nutrition) is the major protein source in the vast majority of current American agricultural animal starter, grower, and finishing or production rations. The ultimate success of US animal production agriculture requires animal diets that support the highest levels of reproductive efficiency. America produces over 103 million cattle, over 200 million hogs, 250 million turkeys, and about 2 billion broiler chickens per year (2008 USDA data). In addition there are approximately 338 million soy-fed egg-laying chickens annually that contribute to the American food supply. All of these agricultural animal production industries are extremely sensitive to reproduction efficiency or other feeding-related health problems. Soy-based American agriculture is operating at record levels of efficiency and production. **Yet, these enormous numbers of soy-fed animals, some of which are much better models of human physiology than isoflavone-treated rodents, were again completely ignored in the Expert Panel's evaluation of soy "toxicity." This is of particular concern in view of the identification of the pig as the best animal model of human isoflavone metabolism (68). American farmers have been performing a pig-soy isoflavone feeding experiment more than 200 million times per year for more that half a century. Given the superior similarity between human and porcine isoflavone metabolism, we question why has this use pattern not been part of the analysis.**

IFC notes with interest the description of the upcoming NIEHS-sponsored IFED study on page 661 of the Expert Panel Draft Report. We also realize that all of the commonly encountered clinical study design

limitations described on page 660 (non-random or unspecified method of assignment to feeding groups, the use of self-selected breast- and formula-feeding mothers, failure to control for the reasons for which soy formula was used, early and inconsistent introduction of solid foods, and masking of parents and outcome assessors to formula assignment) are in fact part of the IFED study design. **We do not believe that the addition of another 100 non-randomized subjects to the soy formula data base justify the cost of this study.**

Finally IFC reiterates its previous recommendations for retrospective research using the vast numbers of subjects of all ages up to 50 years that have been fed soy formulas. We understand the difficulty of retrospective research but, as previously noted, history of safe use analysis for soy formula seems to meet the NRC Institute of Medicine's criteria for valid toxicological analysis (69):

1. Soy formula is used in a traditional medical system.
2. Extensive HCP monitoring of infants assures clinical AEs would be detected and reported.
3. Soy formulas have been and are now ingested.
4. Current and past soy protein isolate ingredients are the same, or similar.
5. Current and traditional soy formula intakes are the same.
6. Current and traditional soy formula compositions very similar.
7. Modern duration of use consistent with historical pattern.
8. Modern indication for use consistent with historical use.
9. Modern target population similar to historical population.

Without a retrospective research effort, it will be at least 3 more decades before we have the chance to build an accurate assessment of any new evidence of potential reproductive and developmental toxicity of soy formula.

As stated earlier in this letter, we take very seriously all issues related to the safety and efficacy of our products. Our conclusions today are essentially the same as in 2006 because the weight of scientific evidence has not changed: the general safety of soy as a dietary component, at levels commonly consumed, has been comprehensively and unequivocally established for both humans and animals. There is no valid clinical data (either historical or new) indicating reproductive or developmental toxicity of soy-based infant formulas. Artificial laboratory animal models testing dietary components at impractically high doses and by other than dietary exposure routes offer little public benefit in the understanding of practical food toxicology, and should not be supported through continued governmental funding.

Soy-based infant formulas safely support appropriate nutrition for normal growth and development in term infants and provide parents and health care professionals with an important infant feeding option. If parents are unnecessarily alarmed about the safety of feeding soy infant formulas, they may choose to feed something else that is neither proven safe nor nutritious and this is not in the best interest of infants.

The IFC appreciates the opportunity to comment and looks forward to the opportunity to participate in the public discussion of the draft report on December 16, 2009.

Respectfully submitted,

Signature Redacted

Mardi K. Mountford, MPH
Executive Vice President

References:

1. Bhatia, J., Greer F.R., American Academy of Pediatrics Committee on Nutrition. Use of soy protein formulas in infant feeding. Pediatrics, 2008; 121(5): 1062-1068.
2. Cordle, C.T. Soy formula for managing infant food allergy and intolerance. Agro FOOD Indus. 2007; 18(2): 26-30.
3. Merritt, R.J., Jenks, B.H. Safety of soy-based infant formulas containing isoflavones: The clinical evidence. J. Nutr. 2004; 134: 1220S-1224S.
4. American Academy of Pediatrics Committee on Nutrition. Pediatric Nutrition Handbook. Elk Grove Village, IL: American Academy of Pediatrics, 1993, pp 190, 360-361.
5. Lasekan, J. B., Ostrom, K. M., Jacobs, J. R., Blatter, M. M., Ndife, L. I., & Gooch, W. M. Growth of newborn, term infants fed soy formulas for one year. Clin. Pediatr. 1999; 38: 563-571.
6. Churella, H. R., Borschel, M. W., Thomas, M. R., Breen, M., & Jacobs, J. Growth and protein status of term infants fed soy protein formulas differing in protein content. J. Am. Coll. Nutr. 1994; 13: 262-267.
7. Mimouni, F., Campaigne, B., Neylan, M., & Tsang, R. C. Bone mineralization in the first year of life in infants fed human milk, cow-milk formula, or soy-based formula. J. Pediatr. 1993; 122: 348-354.
8. Ostrom, K. M., Cordle, C. T., Schaller, J. P., Winship, T. R., Thomas, D. J., Jacobs, J. R., Blatter, M. M., Cho, S., Gooch, W. M., III et al. Immune status of infants fed soy-based formulas with or without added nucleotides for 1 year: part 1: vaccine responses, and morbidity. J. Pediatr. Gastroenterol. Nutr. 2002; 34: 137-144.
9. Cordle, C. T., Winship, T. R., Schaller, J. P., Thomas, D. J., Buck, R. H., Ostrom, K. M., Jacobs, J. R., Blatter, M. M., Cho, S. et al. Immune status of infants fed soy-based formulas with or without added nucleotides for 1 year: part 2: immune cell populations. J Pediatr. Gastroenterol. Nutr 2002; 34: 145-153.
10. Rozman, K.K., Bhatia, J, Calafat, A.M., et al., NTP-CERHR expert panel report on the reproductive and developmental toxicity of soy formula. Birth Defects Res. B. Dev. Reprod. Toxicol. 2006; 77(4): 280-397.
11. Klein K.O., Isoflavones, soy-based infant fiormulas, and relevance to endocrine function. Nutr. Rev. 1998; 56(7): 193-204
12. Setchell, KDR Assessing Risks and Benefits of Genistein and Soy. Env. Health Perspec. 2006; 144(6) A332-A333.
13. Munro, I. C., Harwood, M., Hlywka, J. J., Stephen, A. M., Doull, J., Flamm, W.G. & Adlercreutz, H. Soy isoflavones: a safety review. Nutr. Rev. 2003; 61: 1-33.
14. Strom, B. L., Schinnar, R., Ziegler, E. E., Barnhart, K. T., Sammel, M. D., Macones,G. A et al. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. J. Am. Med. Assoc. 2001; 286: 807-814.
15. AAP-Committee on Nutrition, Soy protein-based formulas: Recommendations for use in infant feeding. Pediatrics 1998; 101: 148-153.
16. Eurpoean soy recommendations ESPGHAN/CON. J. Ped. Gast. Nut. 2006; 42 (4): 352-61
17. Kemp, A.S., Hill D.J., Allen, et al. Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion. Med J Aust. 2008;188(2): 109-112.
18. Bock, S.A., & Atkins, F.M. Patterns of food hypersensitivity during sixteen years of double blind, placebo-controlled food challenges. J. Pediatr. 1990; 117: 561-567.
19. Buts, J.P., Di Sano, C., Hansdorffer S. Clinical Evaluation of the tolerance for a soy-based special milk formula in children with cow's milk protein intolerance/allergy", Minerva Pediatr. 1993; 45(5): 290-213.
20. Cantani, A., Ferrara, M., Rango, V., & Businco, L. Efficacy and safety of soy-protein-formula for feeding babies with atopic dermatitis and cow's milk hypersensitivity. Euro. Rev. Med. Pharma. Sci. 1990; 12: 311-318.
21. Zeiger, R.S., Sampson, H.A., Bock, S.A., Burks, A.W., Harden, K., Noone, S., Martin, D., Leung, S., & Wilson, G. Soy allergy in infants and children with IgE-associated cow's milk allergy. J. Pediatr. 1999; 134: 614-622.
22. Klemola, T., Vanto, T., Juntunen- Backman, K., Kalimo, K., Korpela, R., & Varjonen, E. Allergy to soy formula and extensively hydrolyzed whey formula in infants with cow's milk allergy with a follow up to the age of 2 years. J. Pediatr. 2002; 140: 219-224.
23. Berger-Achituv, S., Shohat, T., Romano-Zelekha, O., et al. Widespread use of soy-based formula without clinical indications. JPGN 2005; 41: 660-666.

24. Agostoni, C., Fiocchi, A., Riva, E., et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. Pediatr Allergy Immunol. 2007; 18(7): 599-606.
25. Mehr, S.S. and Kemp Feeding choice for children with immediate allergic reactions to cows milk protein. Med J Aust. 2008;189(3): 178-179.
26. Caminitti, I., Passalacqua, G., Barberi, S. et al. A new protocol for specific oral tolerance indication in children with IgE-mediated cow's milk allergy. Allergy Asthma Proc. 2009; 30(4): 443-448.
27. Pedrosa, M., Pascual, C.Y., Larco, J.I., Esteban, M.M. Palatability of hydrolysates and Other substitution formulas for cow's milk-allergic children: a comparative study of taste, smell, and texture evaluated by healthy volunteers. J Investig Allergol Clin Immunol. 2006;16(6): 351-356
28. Fine, B.R. and Sehgal, S. Caution with Committee Recommendations for Soy Protein-b Formulas. Pediatrics 2008; 122: 1156.
29. AAP response to Fine, Pediatrics 2008; 122: 1156.
30. Amonette, M.S., Schwartz R. H, et al. Double-Blind, Placebo-Controlled Food Challenges DBPCFC) Demonstrating Acute IgE-Mediated Allergic Reactions to Good Start, Ultrafiltered Good Start, Alfare, Nutramigen and Alimentum in a Seven-Year-Old", Pediatr. Asth. Allergy Immunol. 1991; 5(3): 245-251.
31. Forsyth B.W.C., McCarthy, P.L. Levanthal, J.M. Problems of early infancy, formula changes, and mother's beliefs about their infants. J. Pediatr. 1985; 106: 1012-1017.
32. Iacono G., Merolla R, et al. "Gastrointestinal symptoms in infancy: a population-based retrospective study", Dig. Liver Dis. 2005; 37(6): 432-438.
33. Polack, F.P., Khan, N., Maisels, M.J. Changing partners: the dance of infant formula changes. Clin. Pediatr. 1999; 38(12): 703-708.
34. Berseth, C.L., Johnston, W.H., Stolz, S.I., et al. Clinical response to 2 commonly used switch formulas occurs within 1 day. Clin. Pediatr. (Phila). 2009; 48(1): 58-65.
35. Cao,Y., Calafat, A.M., Doerge, D.R., et al. Isoflavones in urine, saliva, and blood of infants: data from a pilot study on the estrogenic activity of soy formula. J. Expo. Sci. Environ. Epidemiol. 2009; 19(2): 223-34.
36. Bernbaum, J.C., Umbach, D.M., Ragan, N.B., et al. Pilot studies of estrogen-related physical findings in infants. Environ. Health Perspect. 2008;116(3): 416-420.
37. Zung, A., Glaser, T., Kerem, Z., Zadik, Z. Breast development in the first 2 years of life: an association with soy-based infant formulas. J. Pediatr. Gastroenterol. Nutr. 2008; 46(2): 191-195.
38. Gilchrist, J.M., Moore, M.B., Andres, A. et al. Ultrasonographic patterns of reproductive organs in infants fed soy formula: Comparisons to infants fed breast milk and milk formula. J. Pediatrics 2009; Epub @ www.jpeds.com.
39. Jing, H., Pivik, R.T., Gilchrist, J.M., Badger/ T.M. No difference indicated in electroencephalographic power spectral analysis in 3- and 6-month-old infants fed soy- or milk-based formula. Matern. Child Nutr. 2008; 4(2) :136-145.
40. Fattal-Valevski, A., Azouri-Fattal I, Greenstein YJ, Guindy M,, et al. Delayed language development due to infantile thiamine deficiency. Dev. Med. Child. Neurol. 2009a; 51(8): 629-34.
41. Fattal-Valevski, A., Bloch-Mimouni, A., Kivity, S., et al Epilepsy in children with infantile thiamine deficiency. Neurology. 2009b; 73(11): 828-33.
42. de Mattos, A.P., Ribeiro, T.C., Mendes, P.S., et al. Comparison of yogurt, soybean, casein, and amino acid-based diets in children with persistent diarrhea. Nutr Res. 2009; 29(7): 462-9.
43. Ngamphaiboon, J., Chatchatee, P., Thongkaew, T. Cow's milk allergy in Thai children. Asian Pac. J. Allergy Immunol. 2008; 26(4): 199-204.
44. Koplin, J., Dharmage, S.C., Gurrin, L., et al. Soy consumption is not a risk factor for peanut sensitization. J. Allergy Clin. Immunol. 2008;121(6): 1455-9.
45. Yada, K., Yoshida, K., Sakurai, Y., et al. Casein hydrolysate formula-induced liver dysfunction in a neonate with non-immunoglobulin E-mediated cow's milk allergy. J. Investig. Allergol. Clin. Immunol. 2008; 18(1): 67-70.
46. Hoffman, D., Ziegler, E., Mitmesser, S.H., et al. Soy-based infant formula supplemented with DHA and ARA supports growth and increases circulating levels of these fatty acids in infants. Lipids. 2008; 43(1): 29-35.
47. Ostrom, K.M., Jacobs, J.R., Merritt, R.J.., Murray, R.D. Decreased regurgitation with a soy formula containing added soy fiber. Clin. Pediatr. (Phila). 2006; 45(1): 29-36.
48. Pedrosa, M., Pascual, C.Y., Larco, J.I., Esteban, M.M. Palatability of hydrolysates and Other substitution formulas for cow's milk-allergic children: a comparative study of taste, smell, and texture evaluated by healthy volunteers. J. Investig. Allergol. Clin. Immunol. 2006; 16(6): 351-6.

49. Hwang, J-B, Sohn, S.M., Kim, A.S. Prospective follow-up oral challenge in food protein-induced enterocolitis syndrome. Arch. Dis. Child. 2009; 94:425-428.
50. Ballmer-Weber, B.K., Holzhauser, T., Scibilia, J., et al. Clinical Characteristics of soybean allergy in Europe: A double-blind placebo-controlled food challenge study. J. Allergy Clin.Immunol. 2007; 119: 1489-1496.
51. Moreno Villares, J.M., Oliveros Leal, L., Torres Peral, R. Growth in infants with cow's milk allergy. An. Pediatr. (Barc). 2006; 64(3) :244-247.
52. Joeckel, R.J., Phillips, S.K. Overview of infant and pediatric formulas. Nutr. Clin. Pract. 2009; 24(3): 356-362.
53. Turck, D. Soy protein for infant feeding: what do we know? Curr. Opin. Clin. Nutr. Metab. Care. 2007; 10(3): 360-365.
54. Osborne, D.A. and Sinn, J. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database Syst. Rev. 2006 Oct 18; (4):CD003741.
55. Kumar, Y. And Sarvananthan, R. GORD in children. Clinical Evidence 2008; 10: 310.
56. Donovan, S., Andres, A., Mathi, R. Soy formula and isoflavones and the developing intestine. Nutrition Rev. 2009; 67(Suppl. 2): S192-S200.
57. Ozdemir, O., Mete, E., Catal, F., Ozol, D. Food intolerances and eosinophilic esophagitis in childhood. Dig. Dis. Sci. 2009; 54(1): 8-14.
58. Williams, H.C., Grindlay, D.J. What's new in atopic eczema? An analysis of the clinical significance of systematic reviews on atopic eczema published in 2006 and 2007. Clin. Exp. Dermatol. 2008 Nov;33(6):685-8.
59. Hill, D.J., Murch, S.H., Rafferty, K., Wallis, P., Green, C.J. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin. Exp. Allergy. 2007; 37(6): 808-22.
60. Allen, K.J., Hill, D.J., Heine, R.G. Food allergy in childhood. Med J Aust. 2006;185(7): 394-400.
61. Zuidmeer, L., Goldhan, K., Rona, R.J., et al. The prevalence of plant food allergies: A systematic review. J. Allergy Clin. Immunol. 2008; 121: 1210-1218.
62. Greer, F.R., Sicherer, S.H., Burks. A.W., and the AAP Committee on Nutrition and Section on Allergy and Immunology. Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. Pediatrics 2008; 121; 183-191.
63. Chouraqui, J.P., Dupont, C., Bocquet, A. et al., and Comité de nutrition de la Société française de pédiatrie. Feeding during the first months of life and prevention of allergy. Arch Pediatr. 2008; 15(4): 431-442.
64. Comite de nutrition de la Societe francaise de pediatrie, Evidence-based dietetics: what has to be kept in mind for the prescription of infant formulae and follow-on formulae in 2007th? Arch Pediatr. 2007; 14(4): 370-375.
65. Johnson, K., Loomis, G., Flake, D., Harrison, S. Effects of soy protein-based formula in full-term infants. Am. Fam. Physician. 2008; 77(1): 87-8.
66. Badger, T.M., Gilchrist, J.M., Pivik, R.T. The health implications of soy infant formula. Am. J. Clin. Nutr. 2009; 89(5): 1668S-1672S.
67. Andres, A., Donovan, S.M., Kuhlenschmidt, T.B., Kuhlenschmidt, M.S. Isoflavones at concentrations present in soy infant formula inhibit rotavirus infection in vitro. J. Nutrition 2007; 137: 2068-2073.
68. Gu, L., House, S.E., Prior, R.L., Fang, N., et al. Metabolic phenotype of isoflavones differ among female rats, pigs, monkeys, and women. J. Nutrition 2006; 136:1215-1221.
69. "Dietary Supplements: A Framework for Evaluating Safety." The National Academies Press. 2005, pp 137-41.